

BF

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40006 A2(51) International Patent Classification: A61K 31/138,
A61P 25/22

(21) International Application Number: PCT/US01/27801

(22) International Filing Date:
6 November 2001 (06.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/249,010 15 November 2000 (15.11.2000) US
60/265,362 31 January 2001 (31.01.2001) US(71) Applicant (for all designated States except US): ELI
LILLY AND COMPANY [US/US]; Lilly Corporate
Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): THOMASSON,
Holly, Read [US/US]; 204 East 47th Street, Indianapolis,
IN 46205 (US). MICHELSON, David [US/US]; 1264
Clay Spring Drive, Carmel, IN 46032 (US).(74) Agents: TITUS, Robert, D. et al.; Eli Lilly and Company,
Lilly Corporate Center, Indianapolis, IN 46285 (US).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
(utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE
(utility model), DK, DK (utility model), DM, DZ, EC, EE,
EE (utility model), ES, FI, FI (utility model), GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL,
SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG)— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

— without international search report and to be republished
upon receipt of that report
— entirely in electronic form (except for this front page) and
available upon request from the International Bureau

[Continued on next page]

(54) Title: TREATMENT OF ANXIETY DISORDERS

(57) Abstract: Selective norepinephrine reuptake inhibitors are used to treat anxiety disorders, especially obsessive-compulsive disorder.

WO 02/40006 A2



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

-1-

TREATMENT OF ANXIETY DISORDERS

The invention belongs to the fields of pharmaceutical chemistry and central nervous system medicine, and provides a method of treatment for anxiety disorders.

Anxiety disorders represent the most prevalent type of psychiatric disorders in the United States. Anxiety disorders include panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, specific phobia, social phobia, and generalized anxiety disorder. All are characterized by uneasiness, a sense of fearfulness, and distress for no apparent reason. These disorders, if left untreated, reduce the quality of life and productivity of patients suffering from them. In the United States alone, more than 23 million people suffer from anxiety disorders. The cost to society from these disorders is staggering, estimated in 1990 at \$46.6 billion in the United States alone in direct and indirect costs.

Currently available methods for treating anxiety disorders include behavioral therapy, cognitive therapy, and relaxation techniques. These methods typically take a considerable amount of time to achieve their desired effect. To increase the rate of recovery, these methods may be used in combination with one of a number of medications. Currently used medications include benzodiazepines, beta-blockers, buspirone, monoamine oxidase inhibitors, serotonin reuptake inhibitors, and tricyclic antidepressants, all of which have liabilities associated with their use. The benzodiazepines are potentially habit forming and can cause drowsiness; beta-blockers cannot be used if the patient has certain pre-existing medical conditions such as asthma, congestive heart failure, diabetes, vascular disease, hyperthyroidism, or angina pectoris; buspirone has a long induction period before

-2-

its beneficial effects are realized; patients taking monoamine oxidase inhibitors are under strict dietary constraints and there is the potential for drug interactions, low blood pressure, moderate weight gain, reduced sexual response, and insomnia; the serotonin reuptake inhibitors can cause nausea, nervousness, and delayed ejaculation; and the tricyclic antidepressants can cause dry mouth, constipation, blurry vision, difficulty in urination, dizziness, low blood pressure, and moderate weight gain. New methods for treating anxiety disorders are needed which avoid or diminish the liabilities of current therapies.

The present invention provides a method for the treatment of anxiety disorders which comprises administering to a mammal in need of such treatment an effective amount of a selective norepinephrine reuptake inhibitor.

The present invention also provides a method for the prevention of anxiety disorders which comprises administering to a mammal susceptible to said disorders an effective amount of a selective norepinephrine reuptake inhibitor.

The present invention provides a method for the treatment or prevention of anxiety disorders that relies on a novel mechanism of action. This method comprises treating a mammal suffering from or susceptible to anxiety disorders with a compound that is a selective norepinephrine reuptake inhibitor. This mechanism is operative in mammals and the preferred mammal is a human.

A further embodiment of this invention comprises the administration of a composition that exhibits selective norepinephrine reuptake inhibitor activity. The composition may be composed of one or more agents that, individually or together, are selective inhibitors of norepinephrine reuptake.

-3-

The present invention also provides the use of a selective norepinephrine reuptake inhibitor for the preparation of a medicament useful for the treatment or prevention of anxiety disorders.

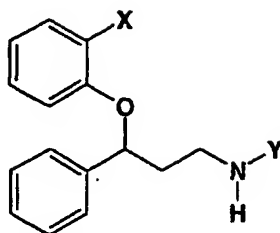
5 The present invention further provides the use of a selective norepinephrine reuptake inhibitor for the preparation of a medicament useful for the treatment of anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder.

10 Many compounds, including those discussed at length below, are selective norepinephrine reuptake inhibitors, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50%
15 effective concentrations of about 1000 nM or less, in the protocol described by Wong et al., *Drug Development Research*, 6, 397 (1985). The norepinephrine reuptake inhibitors useful for the method of the present invention are characterized in being selective for the inhibition of
20 neurotransmitter reuptake relative to their ability to act as direct agonists or antagonists at other receptors. Norepinephrine reuptake inhibitors useful for the method of the present invention include, but are not limited to:

25 Tomoxetine, (R)-(-)-N-methyl-3-(2-methylphenoxy)-3-phenylpropylamine, is usually administered as the hydrochloride salt. Tomoxetine was first disclosed in U.S. Patent #4,314,081. The word "tomoxetine" will be used here to refer to any acid addition salt or the free base of the molecule. See, for example, Gehlert, et al., *Neuroscience Letters*, 157, 203-206 (1993), for a discussion of
30 tomoxetine's activity as a norepinephrine reuptake inhibitor;

-4-

The compounds of formula I:



I

5 wherein X is C₁-C₄ alkylthio, and Y is C₁-C₂ alkyl or a
pharmaceutically acceptable salt thereof. The compounds of
formula I were described in U.S. Patent 5,281,624, of
Gehlert, Robertson, and Wong, and in Gehlert, et al., *Life*
10 *Sciences*, 55(22), 1915-1920, (1995). The compounds are
there taught to be inhibitors of norepinephrine reuptake in
the brain. It is also explained that the compounds exist as
stereoisomers, and that they accordingly include not only
the racemates, but also the isolated individual isomers as
well as mixtures of the individual isomers. For example,
15 the compounds of formula I include the following exemplary
species:

 N-ethyl-3-phenyl-3-(2-methylthiophenoxy)propyl-
amine benzoate;

20 (R)-N-methyl-3-phenyl-3-(2-propylthiophenoxy)-
propylamine hydrochloride;

 (S)-N-ethyl-3-phenyl-3-(2-butylthiophenoxy)propyl-
amine;

 N-methyl-3-phenyl-3-(2-ethylthiophenoxy)propyl-
amine malonate;

25 (S)-N-methyl-3-phenyl-3-(2-tert-butylthiophenoxy)-
propylamine naphthalene-2-sulfonate;

 (R)-N-methyl-3-(2-methylthiophenoxy)-3-phenyl-
propylamine; and

-5-

Reboxetine (EdronaxTM), 2-[α -(2-ethoxy)phenoxy-benzyl]morpholine, is usually administered as the racemate. It was first taught by U.S. Patent 4,229,449, which describes its utility for the treatment of depression.

5 Reboxetine is a selective norepinephrine reuptake inhibitor. The term "reboxetine" will be used here to refer to any acid addition salt or the free base of the molecule existing as the racemate or either enantiomer.

10 While all compounds exhibiting norepinephrine reuptake inhibition are useful for the methods of the present invention, certain are preferred. It is preferred that the norepinephrine reuptake inhibitor is selective for norepinephrine over other neurotransmitters. It is especially preferred that the norepinephrine reuptake
15 inhibitor be selected from tomoxetine, reboxetine, or (R)-N-methyl-3-(2-methylthiophenoxy)-3-phenylpropylamine. The use of tomoxetine hydrochloride for the methods of the present invention is the most preferred embodiment of the present invention.

20 It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free
25 bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

30 Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils

-6-

at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, *b*-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid.

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient including diseases other than that for which the physician is treating the patient. General outlines of the

-7-

dosages, and some preferred dosages, can and will be provided here.

Tomoxetine: from about 5 mg/day to about 200 mg/day; preferably in the range from about 60 to about 150 mg/day; more preferably from about 60 to about 130 mg/day; and still more preferably from about 60 to about 120 mg/day;

Compounds of formula I: from about 0.01 mg/kg to about 20 mg/kg; preferred daily doses will be from about 0.05 mg/kg to 10 mg/kg; ideally from about 0.1 mg/kg to about 5 mg/kg;

Reboxetine: from about 1 to about 30 mg, once to four times/day; preferred, from about 5 to about 30 mg once/day.

All of the compounds concerned are orally available and are normally administered orally, and so oral administration is preferred. However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. Compounds of Formula I may also be administered by the percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs, the convenience of the patient and the caregiver, and other relevant circumstances (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered

-8-

to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

5 The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of
10 the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred
15 compositions and preparations according to the present invention may be determined by a person skilled in the art.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or
20 gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a
25 flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials
30 that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and

-9-

flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

A formulation useful for the administration of R-(-)-N-methyl 3-((2-methylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride (tomoxetine) comprises a dry mixture of R-(-)-N-methyl 3-((2-methylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride with a diluent and lubricant. A starch, such as pregelatinized corn starch, is a suitable diluent and a silicone oil, such as dimethicone, a suitable lubricant for use in hard gelatin capsules. Suitable formulations are prepared containing about 0.4 to 26% R-(-)-N-methyl 3-((2-methylphenyl)oxy)-3-phenyl-1-aminopropane hydrochloride, about 73 to 99% starch, and about 0.2 to 1.0% silicone oil. The following tables illustrate particularly preferred formulations:

-10-

Ingredient (%)	2.5 mg	5 mg	10 mg	18 mg	20 mg	25 mg	40 mg	60 mg
R-(-)-N-methyl 3- ((2-meth- ylphenyl)oxy)-3- phenyl-1- aminopropane hydrochloride	1.24	2.48	4.97	8.94	9.93	12.4 2	19.8 7	22.1 2
Dimethicone	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Pregelatinized Starch	98.2 6	97.0 2	94.5 3	90.5 6	89.5 7	87.0 8	79.6 3	77.3 8

Ingredient (mg/capsule)	2.5 mg	5 mg	10 mg	18 mg	20 mg	25 mg	40 mg	60 mg
R-(-)-N-methyl 3- ((2-meth- ylphenyl)oxy)-3- phenyl-1- aminopropane hydrochloride	2.86	5.71	11.4 3	20.5 7	22.8 5	28.5 7	45.7 1	68.5 6
Dimethicone	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.55
Pregelatinized Starch	225. 99	223. 14	217. 42	208. 28	206. 00	200. 28	183. 14	239. 89
Capsule Fill Weight (mg)	230	230	230	230	230	230	230	310
Capsule Size	3	3	3	3	3	3	3	2

5

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations typically contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 90%

-11-

of the weight thereof. The amount of the compound of formula I present in such compositions is such that a suitable dosage will be obtained. The solutions or suspensions may also include one or more of the following adjuvants: sterile
5 diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene
10 diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Preferred compositions and
15 preparations are able to be determined by one skilled in the art.

The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment, or gel base. The
20 base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bees wax, mineral oil, diluents such as water and alcohol, and emulsifiers, and stabilizers. Topical formulations may contain a concentration of the formula I, or its
25 pharmaceutical salt, from about 0.1 to about 10% w/v (weight per unit volume).

Inhibition or norepinephrine reuptake

The ability of compounds to inhibit the reuptake
30 of norepinephrine may be measured by the general procedure of Wong, *et al.*, *supra*:

Male Sprague-Dawley rats weighing 150-250 gm are decapitated and brains are immediately removed. Cerebral cortices are homogenized in 9 volumes of a medium containing

-12-

0.32 M sucrose and 10 mM glucose. Crude synaptosomal preparations are isolated after differential centrifugation at 1000 x g for 10 minutes and 17,000 x g for 28 minutes. The final pellets are suspended in the same medium and kept in ice until use within the same day.

Synaptosomal uptake of ^3H -norepinephrine is determined as follows. Cortical synaptosomes (equivalent to 1 mg of protein) are incubated at 37°C for 5 minutes in 1 mL Krebs-bicarbonate medium containing also 10 mM glucose, 0.1 mM iproniazide, 1 mM ascorbic acid, 0.17 mM EDTA and 50 nM ^3H -norepinephrine. The reaction mixture is immediately diluted with 2 mL of ice-chilled Krebs-bicarbonate buffer and filtered under vacuum with a cell harvester (Brandel, Gaithersburg, MD). Filters are rinsed twice with approximately 5 mL of ice-chilled 0.9% saline and the uptake of ^3H -norepinephrine assessed by liquid scintillation counting. Accumulation of ^3H -norepinephrine at 4°C is considered to be background and is subtracted from all measurements. The concentration of the test compound required to inhibit 50% of the ^3H -norepinephrine accumulation (IC_{50} values) are determined by linear regression analysis.

Anxiety disorders are a heterogeneous class of diseases. The most common types of anxiety disorders are described in the following paragraphs.

Panic Disorder

Panic disorder is characterized by the sudden onset of intense apprehension, fearfulness, or terror. An attack of panic disorder is unprovoked and may last for a discrete period of time. During these attacks, it is not uncommon for the victim to experience shortness of breath, palpitations, chest pain or discomfort, choking or a smothering sensation, and fear of losing control.

-13-

Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by at least 6 months of persistent and excessive anxiety and worry.
5 It is associated with physical anxiety symptoms such as muscle aches, fatigue, difficulty sleeping, sweating, dizziness, and nausea.

Specific Phobia

10 Specific phobia is a persistent, intense, and irrational fear associated with a particular object or situation that leads to avoidance of that object or situation.

Social Phobia

15 Social phobia is a persistent fear of one or more situations in which the person is exposed to possible scrutiny by others and the person fears that he or she may do something or act in a way that will be humiliating. Social phobias can include extreme shyness.

20

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is characterized by obsessions that cause anxiety and compulsions which serve to neutralize the anxiety. Common obsessions include fear of
25 dirt, germs, or contamination or fear of harming someone; common compulsions are excessive cleaning, counting, double-checking, and hoarding.

Post-Traumatic Stress Disorder

30 Post-traumatic stress disorder is characterized by the re-experiencing of an extremely traumatic event accompanied by symptoms of increased arousal and by avoidance of the stimuli associated with the trauma. Individuals can

-14-

become so preoccupied with the experience that they are unable to lead a normal life.

5 The diseases described above as well as other anxiety disorders contemplated by the method of the present invention are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Version, published by the American Psychiatric Association (DSM). In such cases, the DSM code numbers are supplied below for the convenience of the
10 reader.

	Panic Disorder Without Agoraphobia	DSM 300.01
	Panic Disorder With Agoraphobia	DSM 300.21
	Agoraphobia Without History of Panic	
15	Disorder	DSM 300.22
	Specific Phobia	DSM 300.29
	Social Phobia	DSM 300.23
	Obsessive-Compulsive Disorder	DSM 300.3
	Post-Traumatic Stress Disorder	DSM 309.81
20	Acute Stress Disorder	DSM 308.3
	Generalized Anxiety Disorder	DSM 300.02
	Anxiety Disorder Due to a General Medical Condition	DSM 293.84
	Substance Induced Anxiety Disorder	
25	Alcohol	DSM 291.89
	Amphetamine (or Amphetamine-Like Substance)	DSM 292.89
	Caffeine	DSM 292.89
	Cannabis	DSM 292.89
30	Cocaine	DSM 292.89
	Hallucinogen	DSM 292.89
	Inhalant	DSM 292.89
	Phencyclidine (or Phencyclidine-Like Substance)	DSM 292.89

-15-

	Sedative, Hypnotic, or Anxiolytic	DSM 292.89
	Other [Unknown] Substance	DSM 292.89
	Anxiety Disorder Not Otherwise Specified	DSM 300.00
5	Separation Anxiety Disorder	DSM 309.21
	Sexual Adversion Disorder	DSM 302.79

Any of these disorders, whether presenting alone or in combination in an individual mammal, may be treated or prevented by the method of the present invention. The treatment of Obsessive-Compulsive Disorder is a preferred embodiment of the present invention.

Patients suffering from anxiety disorders also commonly suffer concomitantly from Attention-deficit Hyperactivity Disorder. The patient will receive benefit from the use of norepinephrine reuptake inhibitors in the amelioration of the symptoms of anxiety disorders regardless of whether comorbid conditions are present. Furthermore, a patient suffering from anxiety disorders and Attention-deficit Hyperactivity Disorder will receive benefit in the amelioration of symptoms of both conditions through the method of the present invention. A further embodiment of the present invention, therefore, is a method of treating anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder comprising administering to a patient in need of treatment of both anxiety disorders and Attention-deficit Hyperactivity Disorder an effective amount of a selective norepinephrine reuptake inhibitor.

The method of the present invention is effective in the treatment of patients who are children, adolescents or adults, and there is no significant difference in the symptoms or the details of the manner of treatment among patients of different ages. In general terms, however, for purposes of the present invention, a child is considered to be a patient below the age of puberty, an adolescent is

-16-

considered to be a patient from the age of puberty up to about 18 years of age, and an adult is considered to be a patient of 18 years or older.

5

EXAMPLE 1

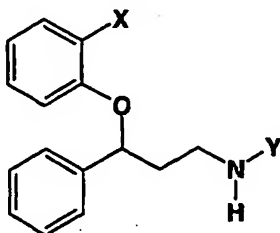
A female subject presented with chronic fingernail biting. The subject was treated with 60 mg of tomoxetine hydrochloride, twice daily for 13 consecutive days. At the time of final assessment the subject demonstrated
10 significant improvement, with healthy appearing fingernails except for one finger. The patient's chronic fingernail biting behavior resumed upon termination of treatment with tomoxetine hydrochloride.

-17-

We claim:

1. Use of a selective norepinephrine reuptake inhibitor for the manufacture of a medicament for the treatment of anxiety of disorders.

2. Use according to Claim 1 wherein the selective norepinephrine reuptake inhibitor is selected from the group consisting of tomoxetine, reboxetine, and a compound of formula I:



I

wherein X is C₁-C₄ alkylthio, and Y is C₁-C₂ alkyl or a pharmaceutically acceptable salt thereof.

3. Use according to Claim 2 wherein the selective norepinephrine reuptake inhibitor is tomoxetine.

4. Use according to Claim 2 wherein the selective norepinephrine reuptake inhibitor is tomoxetine hydrochloride.

5. Use according to any of Claims 1-4 wherein Obsessive-Compulsive Disorder is treated.

6. Use of a selective norepinephrine reuptake inhibitor for the manufacture of a medicament for the treatment of anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder.

7. Use according to Claim 6 wherein the selective norepinephrine reuptake inhibitor is tomoxetine.

-18-

8. Use according to Claim 7 wherein the selective norepinephrine reuptake inhibitor is tomoxetine hydrochloride.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/040006 A3

(51) International Patent Classification⁷: **A61K 31/138**,
31/5375. A61P 25/22

(21) International Application Number: PCT/US01/27801

(22) International Filing Date:
6 November 2001 (06.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/249,010 15 November 2000 (15.11.2000) US
60/265,362 31 January 2001 (31.01.2001) US

(71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **READ, Holly Ann** [US/US]; 204 East 47th Street, Indianapolis, IN 46205 (US). **MICHELSON, David** [US/US]; 1264 Clay Spring Drive, Carmel, IN 46032 (US).

(74) Agents: **TITUS, Robert, D. et al.**; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH.

CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW. ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
24 December 2003

[Continued on next page]

WO 02/040006 A3

(54) Title: TREATMENT OF ANXIETY DISORDERS

(57) Abstract: Selective norepinephrine reuptake inhibitors including tomoxetine and reboxetine are used to treat anxiety disorders, especially obsessive-compulsive disorder.



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/27801

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/138 A61K31/5375 A61P25/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 52518 A (DUBINI ADRIANA ; PHARMACIA & UPJOHN SPA (IT); MCCALL JOHN MICHAEL () 21 October 1999 (1999-10-21)	1
Y	abstract claims 1-7 page 1, line 32 - page 2, line 25 page 3, line 4 - page 5, line 25	1-4
X	----- MANFRED P SCHNEIDER ET AL: "An efficient route to enantiomerically pure antidepressants: Tomoxetine, Nisoxetine and Fluoxetine" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 3, no. 4, April 1992 (1992-04), pages 525-528, XP002109756 ISSN: 0957-4166 page 525, paragraph 1 - paragraph [0002] ----- -/--	1-4



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

16 June 2003

Date of mailing of the international search report

30. 10. 2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Langer, O.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/27801

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOUINARD G ET AL: "FREE COMMUNICATIONS-SESSION A AN EARLY PHASE II CLINICAL TRIAL WITH FOLLOWUP OF TOMOXETINE (Y139603) IN THE TREATMENT OF NEWLY ADMITTED DEPRESSED PATIENTS" PSYCHOPHARMACOLOGY BULLETIN, BETHESDA, MD, US, vol. 21, no. 1, 1985, pages 73-76, XP000603882 ISSN: 0048-5764 page 73, left-hand column, paragraph 1 table 1 -----	1-4
X	WO 97 41878 A (SMITH ROY G ;MERCK & CO INC (US)) 13 November 1997 (1997-11-13) page 5, line 24 - line 31 page 6, line 19 - page 7, line 21 -----	1-4
Y	"TOMOXETINE HYDROCHLORIDE" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 11, 1986, pages 134-135, XP008015974 ISSN: 0377-8282 page 134, right-hand column, paragraph 3 - page 135, left-hand column, paragraph 3 -----	1-4
P,X	WO 01 01973 A (MARSHALL ROBERT CLYDE ;UPJOHN CO (US); WONG ERIK H F (US); BIRGERS) 11 January 2001 (2001-01-11) abstract page 10, line 3 - line 31 -----	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/27801

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Present claim 1 encompasses a genus of compounds (selective norepinephrine reuptake inhibitors) defined only by their function, i.e. their ability to inhibit norepinephrine reuptake, wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or recognisable by one skilled in the art based upon information readily available, the skilled artisan would not know how to make and use compounds that lack a structural definition.

Moreover, present claim 1 relates to a compound defined by reference to a desirable characteristic or property, namely its capability to selectively inhibit norepinephrine reuptake.

The claim covers all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claim also lacks clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported, disclosed and relating to the first invention, namely the use of tomoxetine for the treatment of anxiety disorders other than Obsessive-Compulsive Disorder (OCD) and anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

The expression "anxiety of disorders" in claim 1 is considered to comprise an obvious error, and has been searched as reading "anxiety disorders", see also page 1, lines 5-6.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4 (all partially)

Use of tomoxetine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of anxiety disorders other than Obsessive-Compulsive Disorder (OCD) and other than anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

2. claims: 1, 2 (all partially)

Use of reboxetine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of anxiety disorders other than Obsessive-Compulsive Disorder (OCD) and other than anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

3. claims: 1, 2 (all partially)

Use of a compound of formula (I) or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of anxiety disorders other than Obsessive-Compulsive Disorder (OCD) and other than anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

4. claims: 1-5 (all partially)

Use of tomoxetine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of Obsessive-Compulsive Disorder (OCD), unless accompanied by comorbid Attention-deficit Hyperactivity Disorder (ADHD).

5. claims: 1, 2, 5 (all partially)

Use of reboxetine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of Obsessive-Compulsive Disorder (OCD), unless accompanied by comorbid Attention-deficit Hyperactivity Disorder (ADHD).

6. claims: 1, 2, 5 (all partially)

Use of a compound of formula (I) or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of Obsessive-Compulsive Disorder (OCD), unless accompanied by comorbid Attention-deficit Hyperactivity Disorder (ADHD).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 7, 8, and partially 1-4, 6

Use of tomoxetine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

8. claims: 1, 2, 6 (all partially)

Use of reboxetine or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

9. claims: 1, 2, 6 (all partially)

Use of a compound of formula (I) or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of anxiety disorders with comorbid Attention-deficit Hyperactivity Disorder (ADHD).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/27801

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9952518	A	21-10-1999	IT MI980870 A1	25-10-1999
			AU 755612 B2	19-12-2002
			AU 3635199 A	01-11-1999
			BR 9909476 A	19-12-2000
			CA 2320722 A1	21-10-1999
			CN 1293569 T	02-05-2001
			EA 3546 B1	26-06-2003
			EP 1071418 A2	31-01-2001
			HU 0101748 A2	28-11-2001
			JP 2002511408 T	16-04-2002
			NO 20005131 A	12-10-2000
			NZ 507693 A	29-08-2003
			PL 346294 A1	28-01-2002
			SK 14482000 A3	06-08-2001
			TR 200002970 T2	22-01-2001
			WO 9952518 A2	21-10-1999
			US 6391876 B1	21-05-2002
			ZA 200004480 A	28-02-2002

WO 9741878	A	13-11-1997	AU 2931997 A	26-11-1997
			WO 9741878 A1	13-11-1997

WO 0101973	A	11-01-2001	AU 5633700 A	22-01-2001
			BR 0012136 A	11-06-2002
			CA 2375908 A1	11-01-2001
			CN 1379672 T	13-11-2002
			CZ 20014625 A3	14-08-2002
			EP 1196172 A2	17-04-2002
			HU 0201623 A2	28-09-2002
			JP 2003503450 T	28-01-2003
			NO 20016406 A	19-02-2002
			SK 19382001 A3	02-07-2002
			WO 0101973 A2	11-01-2001
			US 2002061910 A1	23-05-2002
			US 2002086864 A1	04-07-2002
			US 2002107249 A1	08-08-2002
			US 2002128173 A1	12-09-2002
			US 2003040464 A1	27-02-2003
			US 6465458 B1	15-10-2002
			ZA 200110325 A	14-03-2003
